FULL PAPER WILEY-VCH

Obtaining protoanemonin through selective oxidation of D-fructose and 5-(hydroxymethyl)furfural in a self-catalysed reaction

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Abstract: Although different ways of converting 5-(hydroxymethyl)furfural (**1**) to various substrates with high value have been sought, few transformations have obtained building blocks that can be very useful in the area of fine chemistry. Herein, we report the synthesis of protoanemonin (5-methylenefuran-2(5*H*)-one) from D-fructose via compound (**1**), a versatile *γ*-alkylidenebutenolide, using an efficient self-catalysed process with formic acid, with high reaction performance and selectivity (up to 94% yield and 98% conversion from (**1**), while 28% yield from D-fructose). This efficient and simple operational process involved a two-phase aqueous-organic system between chlorinated solvents (CH_xCl_y) and hydrogen peroxide as the initial oxidizing agent. The reaction presents a key cleavage in the 5-hydroxymethyl moiety of (**1**), due to the Baeyer-Villiger oxidation (BVO) process that generates formic acid *in situ*. Ultimately, DFF and HMF were successfully obtained in 80% and 98% yield, respectively, starting from D-fructose and using Preyssler heteropolyacids as Brønsted acid catalysts under an atmosphere of oxygen in the absence of hydrogen peroxide.

Introduction

The transformation of renewable biomass resources into valuable chemicals has received great attention due to their abundance and is a promising sustainable alternative for the production of important intermediates at low cost. One of the main components of the biomass, carbohydrates, can be obtained from the hydrolysis of biopolymers such as cellulose and hemicellulose. These monosaccharides serve as a platform for obtaining multiple substrates, one of the most remarkable being 5-hydroxymethylfurfural (HMF), which can be easily produced by dehydration of pentoses and hexoses, which has been a key intermediate for obtaining important derivatives such as 2,5-diformylfuran (DFF), 2,5-dimethylfuran (DMF), 5-hydroxymethyl-2-furancarboxylic acid (HMFCA), 2,5-furandicarboxylic acid (FDCA), maleic anhydride (MAH), and maleic acid (MA).[1]

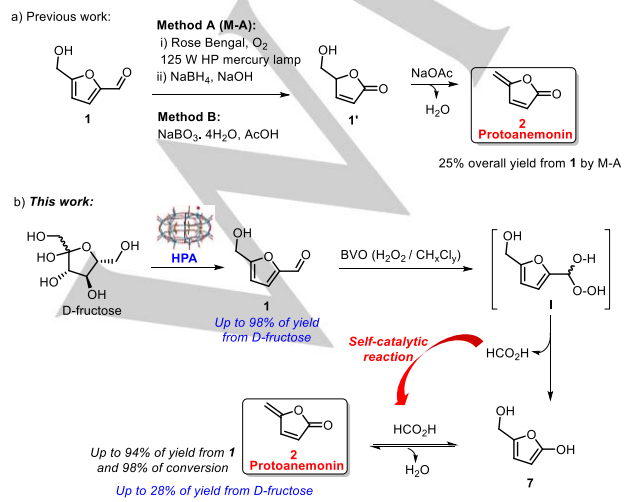
Recently, the oxidation of furfural in the presence of homogeneous acids or acid catalysts and H_2O_2 has been employed to obtain acid anhydrides or dicarboxylic acids, which can be used for the synthesis of diols and lactones. The use of hydrogen peroxide has the advantage of forming distinct reactive species (singlet and triplet oxygen, hydroxyl and perhydroxyl ions and radicals) depending on the decomposition conditions,[2] and the reactions between furans could be manipulated based on the reaction conditions. Overall, the oxidation of furfural to produce dicarboxylic acids has been extensively studied;[3] the yields depend on the type of substituent on the furan ring,[3a,b] reaction temperature, and the amount of oxidant agent employed.[3d] It is importat to note that diverse transformations of HMF into DFF, anhydride maleic, and maleic acid are conducted with vanadium-based catalysts under molecular oxygen atmosphere.[4] A notable aspect of these catalysts is the oxidative scission of the C−C bond between hydroxymethyl fragment and furan ring into HMF for the selective formation of the maleic anhydride and its derivatives, according to the previously reported electron transfer and oxygen transfer reaction mechanism (ET-OT).[4]

Moreover, *γ*-alkylidenebutenolides are versatile building blocks, with interesting reactivity as electrophilic acceptor towards a variety of nucleophiles or as dienophile in Diels-Alder cycloaddition [5] and 1,3-dipolar cycloaddition.[6] This compounds have been used in various transformations and have served as scaffolding to access highly functionalized structures as previously reported in the literature,[7] hence their importance in fine chemistry and drug design. However, various synthetic transformations are required to obtain them, including the intramolecular lactonization of acetylacrylic acid in acid media,[8]

dehydrobromination of *β*,*γ*-dibromo-*γ*-valerolactone with base,[9] and the coupling of (*Z*)-3-iodoacrylic acid with ethynyltrimethylsilane using a heterogeneous and homogeneous catalytic system.[10] Frequently, these methods involve highly functionalized starting materials, polluting reagents, and a low atomic economy due to the large number of steps.

Due to aforementioned, it is of scientific interest to develop a simple and efficient method for obtaining *γ*-alkylidenebutenolides that takes advantage of the availability of biomass. It is notable to emphasize that there are few reports on the transformation of biomass into *γ*-alkylidenebutenolides. Very recently, Zhu *et al*.[11] reported the VO_x/γ-Al_2O_3-catalyzed transformation of the levulinic acid into maleic anhydride at high temperature using an atmosphere of oxygen and helium through the intermediate *γ*-alkylidenebutenolide (protoanemonin), whose formation explaining the high selectivity of the methyl scission during levulinic acid oxidation. Neverthelesses, to the best of our knowledge, there is only one report of 5-(hydroxymethyl)furfural (1) transformation into protoanemonin (**2**). In this investigation, Alibés and co-workers[12] obtained protoanemonin from 5-(hydroxymethyl)furfural through a photo-oxidation process using rose bengal and oxygen to furnish a mixture of lactones, which was subsequently reduced with sodium borohydride to produce 5-hydroxyl-2(5*H*)-furanone intermediate (**1'**) (Scheme 1a). Later, this intermediate was dehydrated using sodium acetate for obtaining protoanemonin (**2**) from (**1**) with an overall yield of 25%. Mliki and Trabelsi reported the synthesis of intermediate (**1'**) in high yield (94%) using sodium perborate and acetic acid, but protoanemonin was not detected using this oxidant agent (Scheme 1a).[13a] It is worth noting that the previously mentioned methods incorporate expensive, difficult to access, and highly contaminating reagents, highlighting that the mechanism for obtaining 5-(hydroxymethyl)furfural incorporates species such as singlet oxygen, affording low selectivity and poor yield towards protoanemonin due to the high functionalization of the furanic substrate used.[13b] As far as we know, this is the first one-pot selective synthesis of protoanemonin (**2**) from D-fructose via 5-(hydroxymethyl)furfural (**1**) by homogeneous auto-catalysis using formic acid generated *in situ* in the Baeyer-Villiger oxidation process with hydrogen peroxide as initial oxidant and chlorinated solvents (CH_xCl_y) (Scheme 1b). High selectivity, conversion and yield was found when directly using 5-(hydroxymethyl)furfural (**1**).

Scheme 1. Synthesis of protoanemonin (**2**) from D-fructose via 5-(hydroxymethyl)furfural (**1**) in a self-catalytic reaction.



Results and Discussion

3.1 Fructose dehydration to obtain DFF and protoanemonin

The dehydration of fructose was studied using Preyssler heteropolyacids and Dowex resin with a 1:1 solvent ratio of DMSO:CH_2Cl_2 (Figure S1). Fructose was converted to HMF with all catalysts for obtaining yields near to 90%. The yield to HMF was similar using Preyssler heteropolyacids, while the Dowex 50W-X8 resin showed a lower yield at initial times, probably due to diffusional problems. Once the HMF was formed, the oxidation process to 2,5-diformylfuran (DFF) began due to aerobic oxidation of the alcohol group of HMF, which is typically observed with acid catalysts.[14] Other by-products were not detected by HPLC analysis. To improve the yield to HMF or DFF, the effect of the reaction atmosphere was studied. The dehydration of fructose was carried out in ambient atmosphere during the first hour and after 1 h of reaction, the reaction atmosphere was changed to O_2 or N_2. Table 1 summarizes the results obtained at 24 h. It can be seen that an oxygen atmosphere did not improve the yield to DFF.

Table 1. Effect of reaction atmosphere in D-fructose dehydration on yield to HMF, DFF, and PA (protoanemonin).[a]

Entry	Catalysts (atmosphere medium)[b]	Solvent ratio DMSO: CH_2Cl_2	Y_{HMF} %	Y_{DFF} %	Y_{PA} %
1	Preyssler (N_2)	1:1	86	6	-
2	Preyssler (O_2)	1:1	98	1	-
3	Preyssler (O_2)	3:0	25	45	-
4	Preyssler (Flow O_2)	3:0	11	80	-
5	Preyssler (H_2O_2)	1:1	67	9	20
6	Preyssler- Mo (H_2O_2)	1:1	56	7	28
7	Dowex resin (H_2O_2)	1:1	41	7	24

[a] Reaction conditions: 3.0 mmol of D-fructose, 40 mg of catalyst, 413 K at 700 rpm for 24 h. [b] After 2 h of reaction the atmosphere was changed.

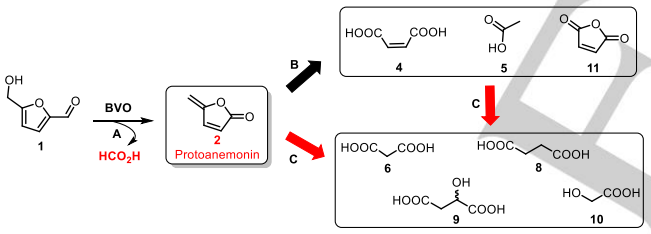
Liu and co-workers[14a] previously demonstrated that molecular oxygen decreased the yields of DFF from fructose in the one-step reaction, which is attributed to the undesired oxidation of fructose by heteropolyacids. However, using a flow of oxygen, the highest DFF yield of 80% with a full conversion of fructose was achieved because the contact time of oxygen with the heteropolyacid was significantly reduced. Likewise, this method has the advantage of using DMSO as solvent, allowing a recovery of the catalyst with CH_2Cl_2 as precipitation solvent. The plug flow systems could be useful in this type of system to improve the yield to DFF. This system has been successfully employed in the synthesis of galacturonic acid to galactaric acid under alkaline conditions.[15] When the reaction was conducted using H_2O_2, an increase in the yield to DFF was not observed; instead, the formation of protoanemonin (PA) was detected, which was evidenced in all acid solids at the lowest yields (<30%) (Table 1, entries 5-7, Figure S2). The formation of PA was explained through the formation *in situ* of formic acid via Baeyer-Villiger oxidation, while the formation of DFF was

conducted via aerobic oxidation. To corroborate this hypothesis, we studied the formation of PA from pure HMF.

3.2 Self-catalysed oxidation process: Generation of formic acid in situ to obtain protoanemonin (2) from HMF

Formic acid presented a higher selectivity than many of the homogeneous and heterogeneous acid catalysts used in oxidation processes involving systems analogous to 5-(hydroxymethyl)furfural (**1**).[16] Hence, we analysed whether an autocatalytic process could take place with the formic acid generated *in situ* by the Baeyer-Villiger oxidation reaction on (**1**) using hydrogen peroxide as the initial oxidant. It is well known that BVO reaction releases formic acid from aldehydes once the rearrangement of the Criegee intermediate occurs,[17] hence the importance of using this reagent generated *in situ* as Brønsted acid catalyst. To analyse in-depth the oxidation process of HMF in the presence of hydrogen peroxide, a general analysis scheme is proposed (Scheme 2). Initially, we studied the preparation of protoanemonin (**2**) through an autocatalytic process with formic acid and the formation *in situ* of performic acid (Scheme 2a). Then, the oxidation of protoanemonin into acetic acid, maleic acid, and maleic anhydride was studied by ^{1}H NMR in $CDCl_3$ (Scheme 2b). Ultimately, more complex oxidation processes for obtaining smaller organic acids such as malonic acid, malic acid, glycolic acid, and succinic acid were unveiled by ^{1}H NMR in DMSO-d_6 (Scheme 2c).

Scheme 2. General analysis of the oxidation process of 5-(hydroxymethyl)furfural (**1**).[a]



[a] Compounds: 5-(hydroxymethyl)furfural (**1**), 5-methylenefuran-2(5*H*)-one (protoanemonin) (**2**), maleic acid (**4**), acetic acid (**5**), maleic anhydride (**11**), malonic acid (**6**), succinic acid (**8**), malic acid (**9**), and glycolic acid (**10**).

When the reaction was conducted in the absence of catalyst (Figure 1a), the results showed that chlorinated solvents (CH_xCl_y) such as dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) allowed a good chemical stabilization of protoanemonin with yields up to 78%. This Brønsted acid catalysis is fundamental to obtain *α,β*-unsaturated lactone, as seen in the HPLC chromatogram in Figure S3. It is important to mention that the use of chlorinated solvents favours the chemical stabilization of protoanemonin due to their non-polar nature, which allows the biphasic oxidation process to be more selective towards the formation of protoanemonin by the Baeyer-Villiger reaction in chlorinated solvents. Taking into account that Baeyer-Villiger oxidation follows a non-ionic mechanism favoured in chlorinated solvents, the choice of the solvent is a noteworthy aspect to consider during the optimization.

The excellent solubility of protoanemonin and 5-(hydroxymethyl)furfural (**1**) in chlorinated solvents and the high conversion in reduced reaction times, allowed us to confirm the noteworthy stabilization of performic acid, the active oxidizing agent, which is generated *in situ* from formic acid.[3b] This peroxy acid could be transferred from the aqueous phase of hydrogen peroxide to the organic phase of chlorinated solvent, improving the interaction with the substrates in the same phase. Remarkably, the most outstanding characteristic of this reaction is the sensitivity to the change in the concentration of hydrogen peroxide, since 3.0 mmol gives the best results with a conversion of 98% and 94% yield of protoanemonin in $CHCl_3$ (Figure1b). An important coversion and yield is also achieved in CH_2Cl_2, with 98% and 81%, respectively (Figure S3b). Drastic changes were observed for a greater number of hydrogen peroxide equivalents, affording lesser yields of protoanemonin (PA).

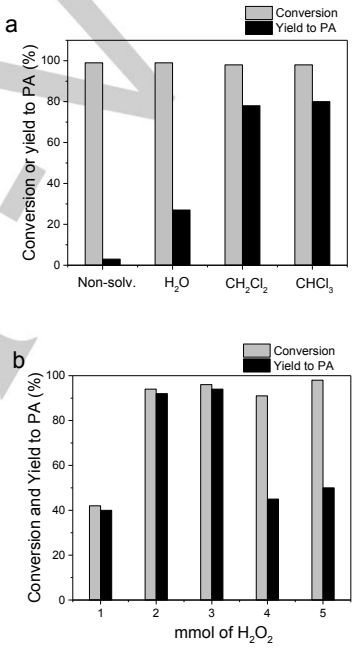
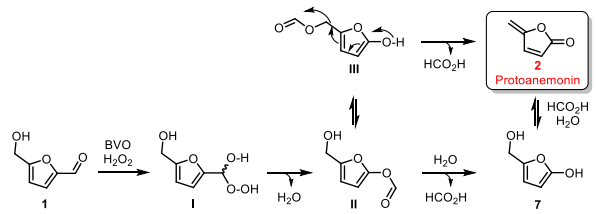


Figure 1. Conversion of HMF and yield of PA as a function of solvent (a), and mmol of H_2O_2 employed (b). Reaction conditions: (a) HMF (1.0 mmol) and H_2O_2 (5.0 mmol) in 3.0 mL of solvent at 333 K and 700 rpm for 4 h, (b) HMF (1.0 mmol), 3.0 mL of $CHCl_3$, and diverse concentrations of H_2O_2 at 333 K and 700 rpm for 4 h.

In another way, continuing with our study of the oxidation process, the identification of diverse oxidation products was determined after obtaining protoanemonin (**2**). For this purpose, an experiment was carried out using HMF (**1**) (1.0 mmol), an excess of hydrogen peroxide (5.0 mmol), and $CDCl_3$ (3.0 mL) as deuterated solvent. The reaction was initially monitored for 8 h by ^{1}H NMR (400 MHz) and ended after 24 h. A plausible reaction mechanism was proposed according to the intermediates detected by ^{1}H NMR (Schemes 3 and 4). It started with the identification of formic acid, acetic acid, maleic acid, and maleic anhydride corresponding to oxidation products that form more rapidly, as depicted in Table 2, Figures 2-3, and S4-S7.
One interesting aspect is the increasing in formic and acetic acids during the course of the reaction (0.5 to 8 h), whose presence drastically decreased after 24 h of reaction. This is

clear evidence that oxidation processes are accompanied by the autocatalysis of those acids, which may form *in situ* performic and peracetic acids,[3b,18] key intermediates to catalyse these oxidation processes.

Scheme 3. Plausible mechanism for the formation of protoanemonin (**2**) from 5-(hydroxymethyl)furfural (**1**).[a]



[a] Compounds (**2**) and (**7**) were identified by ^{1}H NMR analysis of the reaction crude mixture (see Figure 2).

A plausible mechanism for the oxidation of HMF was proposed in Scheme 3, taking in account all oxidation products identified by ^{1}H NMR at the different stages of the reaction (Figures 2 and 3). The oxidation process started with a Baeyer-Villiger reaction between HMF and hydrogen peroxide to form Criegee intermediate (**I**), which is rearranged leading to 5-(hydroxymethyl)furan-2-yl formate (**II**), followed by an intramolecular transesterification to give (5-hydroxyfuran-2-yl)methyl formate (**III**). The formation *in situ* of formic acid was confirmed by ^{1}H NMR at 8.01 ppm, favouring the transformation of HMF into protoanemonin (**2**). All signals in ^{1}H NMR are in agreement with the signals previously reported for this compound.[19] An important aspect is the balance that can occur in acidic aqueous medium between compound (**2**) and 5-(hydroxymethyl)furan-2-ol (**7**), which is also detected by ^{1}H NMR and whose coupling constant confirmed the presence of a furanic ring (J = 3.6 Hz) (*See Supporting Information for details*). The prominent role of the formic acid as Brønsted acid catalyst in different steps of the mechanism is experimentally confirmed.

Table 2. Monitoring of the oxidation reaction of 5-(hydroxymethyl)furfural (**1**) by ^{1}H NMR analysis.[a]

Time (h)	α	Y_2	Y_7	Y_{FA}	Y_3	Y_4	Y_{11}	Y_5	Y_6	Y_8	Y_9	Y_{10}
0.5[b]	34	8	5	2	-	-	-	-	-	-	-	-
1[b]	70	30	6	5	5	-	-	4	-	-	-	-
4[b]	100	60	-	7	9	-	-	11	-	-	-	-
8[b]	100	22	-	14	6	4	12	16	-	-	-	-
24[c]	100	-	-	1	-	22	-	1	30	21	7	13

[a] Reaction conditions: 5-(hydroxymethyl)furfural (**1**) (1.0 mmol), an excess of H_2O_2 (5.0 mmol), and $CDCl_3$ (3.0 mL) as solvent. The reaction was monitored by ^{1}H NMR. [b] Spectrum recorded in $CDCl_3$. [c] Spectrum recorded in DMSO-d_6. α = Conversion (%) and Y = yield (%) to each one of the oxidation products including 5-methylenefuran-2(5*H*)-one (**2**), 5-(hydroxymethyl)furan-2-ol (**7**), formic acid (**FA**), (*Z*)-5-hydroxy-4-oxopent-2-enoic acid (**3**), maleic acid (**4**), maleic anhydride (**11**), acetic acid (**5**), malonic acid (**6**), succinic acid (**8**), malic acid (**9**), and glycolic acid (**10**).

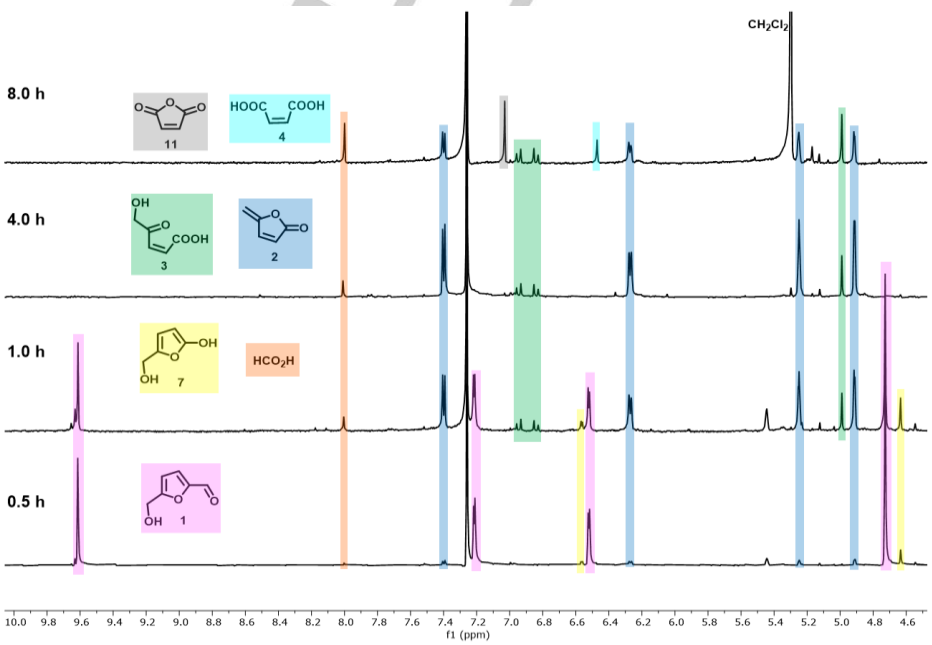
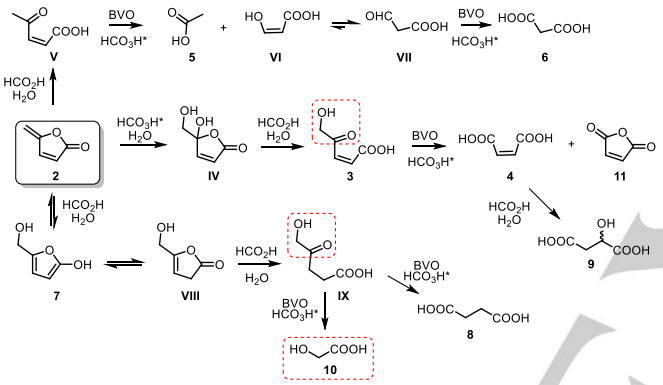


Figure 2. Monitoring of the reaction between HMF (1.0 mmol), an excess of hydrogen peroxide (5.0 mmol), and $CDCl_3$ (3.0 mL) as solvent by ^{1}H NMR analysis. Spectra recorded at 0.5, 1.0, 4.0, and 8.0 h, respectively.

Furthermore, the performic acid generated *in situ* could react with the exocyclic double bond of the protoanemonin (**2**) via a chemoselective epoxidation reaction (Scheme 4),[5a,20] followed by a nucleophilic attack of water for the opening of an epoxide ring to afford 5-hydroxy-5-(hydroxymethyl)furan-2(5*H*)-one (**IV**).[21] It is important to mention that intermediate **IV** is mainly found as tautomer (*Z*)-5-hydroxy-4-oxopent-2-enoic acid (**3**) due to the presence of formic acid in the reaction medium.[22] The tautomer **3** was identified in the ^{1}H NMR spectrum by the *cis* coupling constant between protons of the double bond (J_{cis} = 10.3 Hz) (Figure 2). Later, it could undergo a Baeyer-Villiger oxidation for the formation of maleic acid (**4**) and maleic anhydride (**11**).[4a,23] Ultimately, malic acid (**9**) would form by a formic acid-catalysed hydration into the double bond of maleic acid (**4**).[24] To note that unwanted oxidation products were observed after 24 h of reaction, as shown in Figure 3.

Scheme 4. Plausible mechanism for the formation of protoanemonin (**2**) and diverse organic acids through a complex oxidation process.[a]



[a] 5-Methylenefuran-2(5*H*)-one (**2**), (*Z*)-5-hydroxy-4-oxopent-2-enoic acid (**3**), maleic acid (**4**), acetic acid (**5**), malonic acid (**6**), 5-(hydroxymethyl)furan-2-ol (**7**), succinic acid (**8**), malic acid (**9**), and glycolic acid (**10**) were identified by ^{1}H NMR analysis of the reaction crude mixture (See Figures 2 and 3).

Other different organic acids were identified in the ^{1}H NMR spectra in DMSO-*d*$_6$ after 24 h of reaction (Figure 3). The acetic acid (**5**) and malonic acid (**6**) could be formed by a Baeyer-Villiger oxidation from (*Z*)-4-oxopent-2-enoic acid (**V**),[13] which is generated involving an opening/hydration sequence of protoanemonin (**2**) under an acidic medium.[25] On the other hand, the enol (**7**) could be in equilibrium with its keto form 5-(hydroxymethyl)furan-2(3*H*)-one (**VIII**) (Scheme 4). Considering that medium is acidic until the end of the reaction, as evidenced in the ^{1}H NMR spectrum at 24 h, lactone (**VIII**) could be opened to furnish 5-hydroxy-4-oxopentanoic acid (**IX**), which would participate in a Baeyer-Villiger oxidation to give succinic acid (**8**).[3d] A remarkable aspect is that Baeyer-Villiger oxidation of monocarboxylic acids (**3**) and (**IX**) could produce glycolic acid (**10**) by the migration from the corresponding Criegee intermediate.

The compounds identified in the complex oxidation of HMF show the importance of taking into account the aqueous medium of the biphasic oxidation system, which could not be followed in the first 8 h of reaction by ^{1}H NMR, due to the non-polar nature of the solvent used ($CDCl_3$); nonetheless, it could be monitored by HPLC at 4 h of reaction.

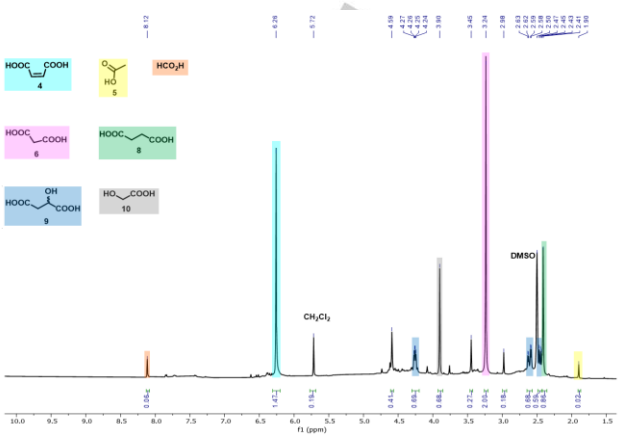


Figure 3. ^{1}H NMR spectrum in DMSO-*d*$_6$ of the reaction crude mixture after 24 h. The characteristic signals of malonic, maleic, malic, glycolic, succinic, acetic, and formic acids are observed and highlighted in the spectrum.

The data obtained by HPLC revealed a higher concentration of protoanemonin (**2**) during the early hours of the reaction in aqueous medium, as well as the incipient formation of organic acids. However, after 24 h the crude reaction monitored by ^{1}H NMR in DMSO-*d*$_6$ confirmed that formic acid self-catalysed oxidation of HMF gave a mixture of organic acids from protoanemonin (**2**) as key intermediate. The formation of these by-products confirmed that protoanemonin can be transformed into valuable building blocks by increasing the number of mmol of hydrogen peroxide (5.0 mmol), indicating the high reactivity of our catalytic system. These findings were observed even at low temperatures, when the reaction between HMF (1.0 mmol) and H_2O_2 (3.0 mmol) in $CHCl_3$ (3.0 mL) for 4 h at 333 K furnished the dilactone, anemonin by the dimerization of protoanemonin (**2**) via a visible light-mediated [2+2] cycloaddition in air.[19] In consequence, the resulting crude was purified by flash column chromatography to afford the monomer protoanemonin (**2**) and its dimer anemonin in 48% and 14% yield, respectively, with an overall yield of 62%. In addition, maleic anhydride (**11**) was obtained in 32% yield (Figures 4 and S8).

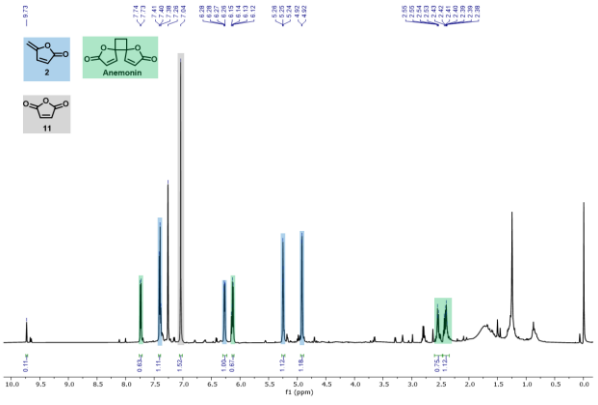


Figure 4. ^{1}H NMR spectrum in $CDCl_3$ of the isolated reaction crude mixture of HMF (1.0 mmol) with H_2O_2 (3.0 mmol) in $CHCl_3$ (3.0 mL) for 4 h.

Conclusion

In conclusion, a *γ*-alkylidenebutenolide (protoanemonin) was obtained from D-fructose via 5-(hydroxymethyl)furfural (**1**) up to 94% yield and 98% conversion from (**1**), while 28% yield from D-fructose. The protocol involves a two-phase aqueous-organic system between chlorinated solvents (CH_xCl_y) and hydrogen peroxide (up to 3.0 equivalent) as the initial oxidizing agent at 333 K for 4 h. Interestingly, this new and simple method allows the 5-hydroxymethyl fragment cleavage of HMF through a Baeyer-Villiger oxidation process that generates formic acid *in situ*, which allows self-catalysis of the oxidation process, by generating *in situ* performic acid. Pleasingly, this one-pot oxidation process has not been previously reported and is an alternative for obtaining *γ*-alkylidenebutenolide of high benefit in the areas of fine chemistry and drug design. It is worth noting that the reaction depends on the concentration of H_2O_2, since a high number of equivalents leading to diverse oxidation products such as malic acid, maleic acid, malonic acid, among others. During this oxidation study, it was also observed that D-fructose can be efficiently transformed into DFF and HMF with 80% and 98% yield, respectively, in the presence of a Preyssler heteropolyacid, which acts as a Brønsted catalyst under an atmosphere of oxygen in the absence of H_2O_2.

Experimental Section

2.1 Materials

The solvents and reagents were purchased from Sigma-Aldrich and used without further purification. 5-(Hydroxymethyl)furfural (**1**) (≥99%), 2,5-furandicarboxaldehyde (97%), hydrogen peroxide (30%), dichloromethane (reactive grade), chloroform (reactive grade), acetone (99.9%), acetonitrile (≥99%), chloroform-*d* (99.8 atom % D, contains 1% (v/v) TMS) and dimethyl sulfoxide-d_6 (99.9 atom % D, contains 1% (v/v) TMS) were employed. Deionized water (Milli-Q, >18 MU cm) was used in all experiments. The preparation of Preyssler heteropolyacids has been broadly described by our research group,[26] as well as sulfonated silica.[26] In addition, commercially available Dowex 50W-X8 ion-exchange resin was employed.

2.2 Aerobic oxidation of HMF from D-fructose to obtain DFF

Crude HMF was obtained using 1.0 mmol of D-fructose solution in DMSO:CH_2Cl_2 at 140 °C at 700 rpm for 1 h in the presence of an acid catalyst (Preyssler HPA, Preyssler-Mo HPA, and Dowex resin). Subsequently, H_2O_2 was added to the reaction mixture at 1 h and was maintained at the same temperature under stirring for 24 h. The effects of different solvent ratios were evaluated.

2.3 Obtaining protoanemonin from HMF by a self-catalysed oxidation process

The oxidation of commercial HMF was studied in a glass reactor fitted with a reflux condenser at atmospheric pressure. The initial reaction conditions were 1.0 mmol of HMF, 5.0 mmol of H_2O_2, and 3.0 mL of solvent, maintained at 333 K and 700 rpm for 24 h. The effects of solvent (CH_2Cl_2, $CHCl_3$, H_2O, acetone, and acetonitrile), hydrogen peroxide concentration (1.0, 2.0, 3.0, 4.0, and 5.0 mmol), Brønsted acid catalyst (Preyssler HPA, sulfonated silica, and Dowex resin), and reaction time (0.5, 1, 4, 8, and 24 h) were evaluated. When the effect of the catalyst on the oxidation reaction was studied, 50 mg of each catalyst was added to the reaction mixture. Once the crude was obtained, it was filtered and analysed by HPLC and NMR spectroscopy, as appropriate.

2.4 Characterization

When the reaction ended, the catalyst was recovered by filtration, and the liquid phase was analysed in a HPLC Knauer-azura equipment with a Knauer Eurokat H^+ column (300 × 4 mm, 10 µm) using a UV detector at 254 nm to quantify HMF and other by-products. The column temperature was maintained at 313 K, and the mobile phase was a solution of H_2SO_4 (4.0 mmol) in water with a flow rate of 0.2 mL/min. The retention times for HMF, DFF, and PA were 27, 32, and 38 min, respectively. Some conversions and selectivities were determined by the relative peak area of substrates and products using a normalization method in HPLC. It is important to mention that some conversions and yields were determined by ^{1}H NMR analysis of the reaction crude mixtures. NMR spectra were recorded at 400 MHz (^{1}H) and 101 MHz (^{13}C) at 298 K. NMR spectroscopic data were obtained in $CDCl_3$ and DMSO-d_6 using the residual non-deuterated signal for ^{1}H NMR (δ = 7.26 and 2.50 ppm, respectively) and the deuterated solvent signal for ^{13}C NMR spectroscopy (δ = 77.16 and 39.52 ppm, respectively) as internal references. DEPT spectra were used for the assignment of carbon signals. Two-dimensional NMR experiments (HSQC, HMBC and COSY) were employed to determine the structure of some oxidation products formed during the oxidation process. Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. The following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet and m = multiplet.

Acknowledgements

We gratefully acknowledge to the Dirección de Investigaciones at the Universidad Pedagógica y Tecnológica de Colombia (project SGI-2829) and Universidad de los Andes for financial support. J.P. acknowledges support from the Science Faculty (project INV-2019-84-1800). O.H.P.C. acknowledges to the Departamento Administrativo de Ciencia y Tecnología e Innovación (Colciencias, convocatoria 733 de 2015). G.P.R. acknowledges to the CONICET, UNLP and CIC.

Keywords: Baeyer-Villiger oxidation • biomass • self-catalysis • 5-(hydroxymethyl)furfural • 2,5-furandicarboxaldehyde • protoanemonin

[1] a) A. A. Rosatella, S. P. Simeonov, R. F. M. Frade, C. A. M. Afonso, *Green Chem.* **2011**, *13*, 754–793; b) R.-J. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, J. G. de Vries, *Chem. Rev.* **2013**, *113*, 1499–1597; c) K. I. Galkin, V. P. Ananikov, *ChemSusChem*, **2019**, *12*, 2976–2982; d) C. Xu, E. Paone, D. Rodríguez-Padrón, R. Luque, F. Mauriello, *Chem. Soc. Rev.* **2020**, *49*, 4273–4306; e) W. Fan, C. Verrier, Y. Queneau, F. Popowycz, *Curr. Org. Synth.* **2019**, *16*, 583–614; f) A. Rodríguez-Montaña, M. Brijaldo, L. Rache, L. Silva, L. Esteves, *Ciencia en Desarrollo* **2020**, *11*, 63-80.

[2] L. A. Badovskaya, V. V Poskonin, L. V Povarova, *Russ. Chem. Bull.* **2017**, *66*, 593–599.

[3] a) X. Li, B. Ho, D. S. W. Lim, Y. Zhang, *Green Chem.* **2017**, *19*, 914–918; b) Y. Lou, S. Marinkovic, B. Estrine, W. Qiang, G. Enderlin, *ACS Omega* **2020**, *5*, 2561–2568; c) C. Van Nguyen, J. R. Boo, C.-H. Liu, T. Ahamad, S. M. Alshehri, B. M. Matsagar, K. C.-W. Wu, *Catal. Sci. Technol.* **2020**, *10*, 1498–1506; d) H. Choudhary, S. Nishimura, K. Ebitani, *Appl. Catal. A Gen.* **2013**, *458*, 55–62.

[4] a) Z. Du, J. Ma, F. Wang, J. Liu, J. Xu, *Green Chem.* **2011**, *13*, 554–557; b) J. Lan, J. Lin, Z. Chen, G. Yin, *ACS Catal.* **2015**, *5*, 2035–2041; c) L. Chai, X. Hou, X. Cuia, H. Lia, N. Zhanga, H. Zhanga, C. Chena, Y.

Wanga, T. Deng, *Chem. Eng. J.* **2020**, *388*, 124187, d) C. Carlini, P. Patrono, A. M. Raspolli Galletti, G. Sbrana, V. Zima, *Appl. Catal. A Gen.* **2005**, *289*, 197–204.

[5] a) D. Alonso, J. Orti, V. Branchadell, A. Oliva, R. M. Ortuno, J. Bertran, J. Font, *J. Org. Chem.* **1990**, *55*, 3060–3063; b) D. Alonso, J. Font, R. M. Ortuno, *J. Org. Chem.* **1991**, *56*, 5567–5572.

[6] a) F. Rodier, M. Rajzmann, J. L. Parrain, G. Chouraqui, L. Commeiras, *Chem.-A Eur. J.* **2013**, *19*, 2467–2477; b) D. Insuasty, J. Castillo, D. Becerra, H. Rojas, R. Abonia, *Molecules* **2020**, *25*, 505.

[7] a) V. Kotzabasaki, G. Vassilikogiannakis, M. Stratakis, *Org. Lett.* **2016**, *18*, 4982–4985; b) Z. Ahmed, P. Langer, *J. Org. Chem.* **2004**, *69*, 3753–3757; c) P. Pal, S. Nanda, *Org. Lett.* **2017**, *19*, 1164–1167.

[8] E. Shaw, *J. Am. Chem. Soc.* **1946**, *68*, 2510–2513.

[9] T. Hirabayashi, K. Yokota, *Polym. J.* **1989**, *21*, 341–346.

[10] D. Rambabu, S. Bhavani, K. S. Nalivela, S. Mukherjee, M. V. B. Rao, M. Pal, *Tetrahedron Lett.* **2013**, *54*, 2151–2155.

[11] R. Zhu, A. Chatzidimitriou, B. Liu, D. J. Kerwood, J. Q. Bond, *ACS Catal.* **2020**, *10*, 1555–1565.

[12] R. Alibés, J. Font, A. Mulá, R. M. Ortuño, *Synth. Commun.* **1990**, *20*, 2607–2615.

[13] a) K. Mliki, M. Trabelsi, *Res. Chem. Intermed.* **2016**, *42*, 8253–8260; b) D. Noutsias, A. Kouridaki, G. Vassilikogiannakis, *Org. Lett.* **2011**, *13*, 1166–1169.

[14] a) R. Liu, J. Chen, L. Chen, Y. Guo, J. Zhong, *ChemPlusChem* **2014**, *79*, 1448–1454; b) G. Lv, H. Wang, Y. Yang, T. Deng, C. Chen, Y. Zhud, X. Hou, *Green Chem.* **2016**, *18*, 2302–2307.

[15] F. van der Klis, L. Gootjes, J. van Haveren, D. S. van Es, J. H. Bitter, *React. Chem. Eng.* **2018**, *3*, 540–549.

[16] X. Li, X. Lan, T. Wang, *Catal. Today* **2016**, *276*, 97–104.

[17] a) N. Mora-Diez, S. Keller, J. R. Alvarez-Idaboy, *Org. Biomol. Chem.* **2009**, *7*, 3682–3690; b) G.-J. Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.* **2004**, *104*, 4105–4124.

[18] J. Kim, T. Zhang, W. Liu, P. Du, J. T. Dobson, C.-H. Huang, *Environ. Sci. Technol.* **2019**, *53*, 13312–13322.

[19] C. Crey, P. Dumy, J. Lhomme, M. Kotera, *Synth. Commun.* **2003**, *33*, 3727–3732.

[20] a) K. Tanaka, F. Uchiyama, K. Sakamoto, Y. Inubushi, *J. Am. Chem. Soc.* **1982**, *104*, 4965–4967; b) I. Martínez, A. E. Andrews, J. D. Emch, A. J. Ndakala, J. Wang, A. R. Howell, *Org. Lett.* **2003**, *5*, 399–402.

[21] J. Shi, Y. J. Zeng, B. Zhang, F. L. Shao, Y. C. Chen, X. Xu, Y. Sun, Q. Xu, R. X. Tan, H. M. Ge, *Chem. Sci.* **2019**, *10*, 3042–3048.

[22] a) T. S. A. Heugebaert, C. V Stevens, C. O. Kappe, *ChemSusChem* **2015**, *8*, 1648–1651; b) K. Csatayová, S. G. Davies, A. M. Fletcher, J. G. Ford, D. J. Klauber, P. M. Roberts, J. E. Thomson, *J. Org. Chem.* **2014**, *79*, 10932–10944.

[23] X. Li, Y. Zhang, *Green Chem.* **2016**, *18*, 643–647.

[24] a) W. Chen, X. Chen, S. Yi, *ACS Omega* **2019**, *4*, 8274–8281; b) R. W. P. Ortiz, C. Benincá, L. Cardozo-Filho, E. F. Zanoelo, *Ind. Eng. Chem. Res.* **2017**, *56*, 3873–3879.

[25] S. Seltzer, K. D. Stevens, *J. Org. Chem.* **1968**, *33*, 2708–2711.

[26] a) O. H. P. Cuervo, H. A. Rojas, L. A. Santos, T. C. Ramalho, G. P. Romanelli, J. J. Martínez, *ChemistrySelect* **2018**, *3*, 1–9; b) A. Paez, H. A. Rojas, O. Portilla, C. A. M. Afonso, G. P. Romanelli, J. J. Martínez, *ChemCatChem* **2017**, *9*, 3322–3329; c) J. J. Martínez, E. Nope, H. Rojas, M. H. Brijaldo, F. Passos, G. Romanelli, *J. Mol. Catal. A Chem.* **2014**, *392*, 235–240; d) J. J. Martínez, L. Silva, H. A. Rojas, G. P. Romanelli, L. A. Santos, T. C. Ramalho, M. H. Brijaldo, F. B. Passos, *Catal. Today* **2017**, *296*, 118–126; e) S. Chaparro, H. A. Rojas, J. C. Castillo, J. Portilla, G. P. Romanelli, A. Pineda, A. M. Elsharif, J. J. Martínez, R. Luque, *ACS Sustainable Chem. Eng.* **2020**, Article ASAP doi: 10.1021/acssuschemeng.0c04429; f) J. J. Murcia Mesa, J. R. Guarín Romero, Á. C. Cely Macías, H. A. Rojas Sarmiento, J. A. Cubillos Lobo, M. C. Hidalgo López, J. A. Navío Santos, *Ciencia en Desarrollo* **2017**, *8*, 109–117.

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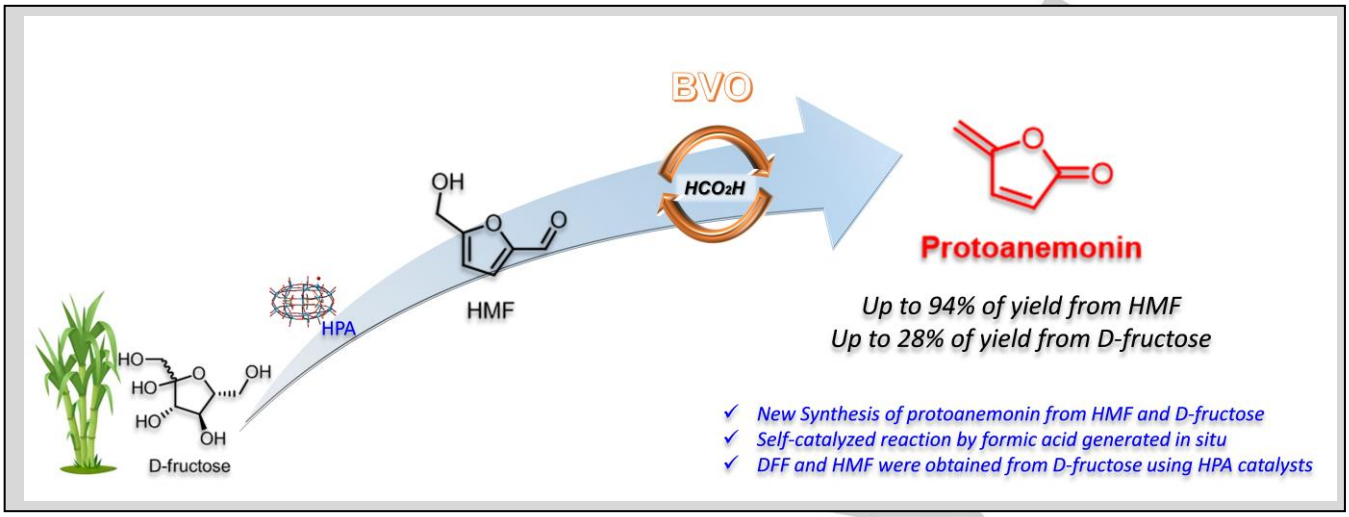

Formic acid self-catalyzed reaction: the synthesis of 2,5-diformylfuran (DFF) and 5-(hydroxymethyl)furfural (HMF) in high yields and selectivities from D-fructose using Preyssler heteropolyacids as Brønsted catalysts is described. Moreover, a new and simple synthesis of protoanemonin with 94% yield and 98% conversion from HMF through a Baeyer-Villiger oxidation with hydrogen peroxide in chlorinated solvents has been developed. Ultimately, studies by NMR supported our hypothesis that formic acid generated *in situ* allowed the formation of protoanemonin through a self-catalyzed process.